Synthesis and Isolation of Bromo-β-carbolines Obtained by Bromination of β-Carboline Alkaloids

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β-Carbolines (**1**-**5**) undergo electrophilic aromatic substitution with *N*-bromosuccinimide under different experimental conditions. Although 6-bromo-nor-harmane (**1a**) obtained by bromination of nor-harmane (**1**) was isolated and fully characterized sometime ago, the other bromoderivatives of nor-harmane (**1b**-**1e**) and harmane (**2a**-**2e**) were partially described as part of the reaction mixtures. The preparation and subsequent isolation, purification and full characterization of **1b**, **1c**, **1d**, **1e**, **2a**, **2b**, **2c**, **2d**, **2e** are reported (mp, R_f, ^{1}H-nmr, ^{13}C-nmr and ms) together with the preparation, isolation and charaterization, for the first time, of the bromoderivatives obtained from harmine (**3a**-**3e**), harmol (**4a**, **4b**) and 7-acetylharmol (**5a**-**5c**). As brominating reagent *N*-bromosuccinimide and *N*-bromosuccinimide-silica gel in dichloromethane and in chloroform as well as the β-carboline - *N*-bomosuccinimide solid mixture have been used and their uses have been compared. Semiempirical AM1 and PM3 calculations have been performed in order to predict reactivity in terms of the energies of HOMO, HOMO-LUMO difference and in terms of the charge density of β-carbolines (**1**-**5**) and bromo-β-carbolines (**1a**-**1e**, **2a**-**2e**, **3a**-**3e**, **4a**, **4b**, **5a**, **5b** and **5c**) (Scheme 1). Theoretical and experimental results are discussed briefly.

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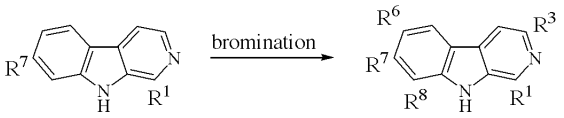
Introduction

As part of our study of the photochemistry of commercially available azacarbazoles (β-carbolines) [1] and their potential use as matrices (photosensitizers) in matrix assisted ultraviolet laser desorption/ionization time-of-flight mass spectrometry (uv-maldi-tof ms) [2], we decided to examine the behavior of substituted β-carbolines. To begin with, preparation of nitro-β-carbolines [3] and bromo-β-carbolines was selected because, as it is known, for aromatic molecules these groups as substituents induce strong modifications on the acid-base properties in the ground and electronic excited state and on the nature (π,π^*; n,π^*), multiplicity (singlet, S_1; triplet, T_1), time of life (τ_{S1}; τ_{T1}) and efficiency of population (ϕ) of the electronic excited states [4,5].

The present study reports the preparation of bromo derivatives from β-carbolines (Scheme 1, nor-harmane (**1**), harmane (**2**), harmine (**3**), harmol (**4**) and 7-acetylharmol (**5**)) using *N*-bromosuccinimide as brominating reagent providing for the first time bromo-β-carbolines **3a**, **3b**, **3c**, **3d**, **3e**, **4a**, **4b**, **5a**, **5b**, and **5c**. We also describe in detail the use of chromatographic methods (tlc, preparative chromatographic folders and column chromatography) in order to (i) follow the bromination reaction, (ii) determine the yield of the reactions and (iii) isolate for complete characterization (elemental analysis, R_f, mp, ^{1}H-nmr, ^{13}C-nmr and ms) of the above mentioned bromo-β-carboline derivatives as well as the derivatives **1b**, **1c**, **1d**, **1e**, **2a**, **2b**, **2c**, **2d** and **2e** previously described [6,7].

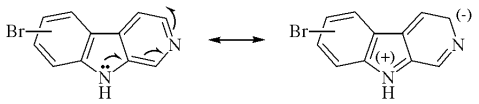
According to our knowledge, *N*-bromosuccinimide and silica gel reagent was used for the bromination of nor-harmane and harmane [6]. As the reagent was not selective a mixture of products was obtained. The authors suggested that as in the reaction mixtures no one product predominated recrystallization was not practical and the products were too impure for mp and microanalysis, so they were characterized only by ^{1}H-nmr and hrms. In 1987, Rinehart

Scheme 1



Compound	R^1	R^7	Compound	R^1	R^3	R^6	R^7	R^8
1	H	H	**1a**	H	H	Br	H	H
2	Me	H	**1b**	H	H	H	H	Br
3	Me	MeO	**1c**	H	H	Br	H	Br
4	Me	HO	**1d**	H	Br	Br	H	H
5	Me	AcO	**1e**	H	Br	Br	H	Br
			2a	Me	H	Br	H	H
			2b	Me	H	H	H	Br
			2c	Me	H	Br	H	Br
			2d	Me	Br	Br	H	H
			2e	Me	Br	Br	H	Br
			3a	Me	H	Br	MeO	H
			3b	Me	H	H	MeO	Br
			3c	Me	H	Br	MeO	Br
			3d	Me	Br	Br	MeO	H
			3e	Me	Br	Br	MeO	Br
			4a	Me	H	Br	HO	H
			4b	Me	H	H	HO	Br
			5a	Me	H	Br	AcO	H
			5b	Me	H	H	AcO	Br
			5c	Me	Br	Br	AcO	H

Scheme 2



et al., in order to characterize the alkaloid eudistomin N (6-bromo-nor-harmane, **1a**), isolated from antiviral Caribbean tunicate *Eudistoma olivaceum*, described the synthesis of this bromo-β-carboline and its complete characterization (mp, uv, ir, ^{1}H-nmr, ^{13}C-nmr, ms and elemental analysis) [7]. It is interesting to point out that only the isolation and full characterization of 6-bromo-nor-harmane is reported in the above mentioned reference [7].

Results and Discussion.

In order to prepare bromo-β-carbolines we decided to use the classical method with *N*-bromosuccinimide (NBS) in dichloromethane [8,9]. When the brominating reagent to β-carboline (nor-harmane) molar ratio was 1:1, 6-bromo-nor-harmane (**1a**) and 8-bromo-nor-harmane (**1b**) were the main products formed in 85% and 10%, respectively (Table I, entry a). Also in the reaction mixture 6,8-dibromo-nor-harmane (**1c**) was detected (5%). When two equivalents of brominating reagent were used (1:2 molar ratio), dibromo-nor-harmane derivatives **1c** and **1d** were obtained as main products and also the corresponding tribromoderivative, 3,6,8-tribromo-nor-harmane **1e**, was obtained in a ignificant amount (see Table I, entry b, 50%, 13% and 37% respectively).

When harmane (**2**) was treated at room temperature with the brominating reagent (NBS) in molar ratios 1:1 and 1:2, the mono-bromo derivatives **2a** and **2b** were obtained as the main products in the former (Table I, entry e, 83% and 12%) while the dibromo-derivatives **2c** and **2d** and the tribromo-derivative **2e** were obtained as the main products in the latter (Table I, entry f, 22%, 39% and 39%). This partial selectivity of the brominating reaction and the clear difference in the composition of the reaction mixtures were also observed when harmine was treated with NBS in 1:1 and 1:2 molar ratio (Table I, entries i and j).

Taking into account that the bromination of nor-harmane and harmane were attempted by Smith *et al*., [6] by using NBS and silica gel as reagent, we decided to study the use of NBS - silica gel system as reagent for the bromination of β-carbolines. As can be seen in Table I, entries c, d, g, h, k and l, similar product distribution were observed with and without silica gel although these experiments required

Table I

Bromination of β-Carbolines by Using NBS
Products (% yield) [a]

Experiment	β-Carboline:NBS (molar ratio) [b]	Time (hours)	Conversion (%)					
Nor-harmane (**1**)								
				1a	**1b**	**1c**	**1d**	**1e**
a	1:1	24	90	85	10	5	-	-
b	1:2	24	100	-	-	50	13	37
c	1:1/silica-gel	48	100	61	10	14	9	6
d	1:2/silica-gel	48	100	19	-	30	22	28
Harmane (**2**)								
				2a	**2b**	**2c**	**2d**	**2e**
e	1:1	24	100	83	12	5	-	-
f	1:2	24	100	-	-	22	39	39
g	1:1/silica-gel	48	100	55	5	27	13	-
h	1:2/silica-gel	48	100	18	-	43	15	24
Harmine (**3**)								
				3a	**3b**	**3c**	**3d**	**3e**
i	1:1	24	100	84	11	5	-	-
j	1:2	24	100	-	-	60	8	32
k	1:1/silica-gel	48	100	72	12	16	-	-
l	1:2/silica-gel	48	100	39	-	37	21	3
Harmol (**4**)								
				4a	**4b**			
m	1:1	24	96	-	100			
n	1:1/silica-gel	48	93	6	94			
7-Acetylharmol (**5**)								
				5a	**5b**		**5d**	
o	1:1	24	100	6	94		-	
p	1:1/silica-gel [c]	48	100	13	67		5	

[a] Quantitative column chromatography análisis; [b] β-Carboline to NBS molar ratio; [c] Compounds **4a** was obtained in 15 % yield.

Table II

Reaction Conditions and Observed Products in Solid State Bromination Reactions of β-Carbolines with NBS [a]

Experiment/Time	Time (minutes)/Products (% conversion)																
	2	3	5	7	11	13	15	18	21	27	35	45	60	80	95	60x24	
nor-harmane/NBS (1:1)	-	-	-	-	-	-	-	-	-	**1a**	**1a**	**1a**	**1a**	**1a**	**1a+1b**	**1a+1b+1c**	
Conv (%)	0	0	0	0	0	0	0	0	0	30	50	60	80	80	100	100	
Harmine/NBS (1:1)	**3a**	**3a**	**3a**	**3a+3b**	**3a+3b**	**3a+3b**	**3a+3b**	**3a+3b**	**3a+3b**	**3a+3b**	**3a+3b**	**3a+3b**	**3a+3b+3c**	**3a+3b+3c+3d**	**3a+3b+3c+3d**	**3a+3b+3c+3d**	
Conv. (%)	30	50	70	100	100	100	100	100	100	100	100	100	100	100	100	100	

[a] β-Carbolines/NBS (1:1 molar ratio); experiments were performed at room temperature; melting points: nor-harmane, 200°; **1a**, 263-265°; **1b**, 248-250°; **1c**, >300°; **1d**, 273-275°; **1e**, 280-282°. Harmine, 261°; **2a**, 248-250°; **2b**, 201-204°; **2c**, 248-250°; **2d**, 255-257°; **2e**, 233-235°.

48 hours instead of 24 hours to reach a 100% of substrate conversion. NBS and silica gel as reagent provided for nor-harmane and harmane bromo-derivatives as products in regoiselective reactions which were quite different than those previously reported [6]. Smith *et al*., [6] mentioned that the bromoderivatives **1a** - **1e** and **2a** - **2e** were obtained altogether and that they could not get each bromoderivative as a pure compound.

A different result was observed when harmol was brominated with NBS in dichloromethane, at room temperature. The 8-bromo-derivative (8-bromoharmol, **4b**) was the major product obtained (Table I, entry m). In a similar manner, when the 7-acetyl derivative of harmol, 7-acetylharmol **5**, was brominated with NBS in dichloromethane, the corresponding 8-bromoderivative **5b** was obtained as the principal product together with a small amount of the 6-bromo-7-actylharmol **5a** (Table I, entry o).

From the reaction mixtures, each bromoderivative was isolated and purified by combining different chromatographic techniques (silica gel - column chromatography and silica gel - preparative chromatographic folders) and crystallization. After that, each derivative was ready for its full characterization.

Solid State Bromination with *N*-Bromosuccinimide

N-Bromosuccinimide (NBS) is an important reagent not only for bromination but also for a host of other reactions [8,9]. Depending upon the nature of the reactant and reaction conditions, in solution, NBS reacts differently with many aromatic compounds. Being a constant source of Br_2 at very low concentrations, NBS is used extensively in bromination reactions involving radical substitution, electrophilic addition and substitution pathways while oxidation reactions are not that uncommon [10]. However, many of these reactions lead to multiple products [8,9]. High product selectivity is generally not observed in the solution reactions, even when NBS - silica gel reagent is used [6]. Recently, solid state NBS bromination of phenols [10,11], hydroquinones [10], anilines [11] and nitro aromatic compound [11] have been reported. Thus, the aim of the present study is to compare the bromination reaction of β-carbolines in solution and in solid state

Reaction Conditions.

One of the important postulates for any solid state reaction is that optimum yield is obtained when the reaction temperature is well below the melting point of the reactant (preferably below by ~ 30°) [11-14]. This is one of the important postulates for any solid state reaction [13,14]. In general, solid state NBS brominations are highly exothermic [10,11]. In spite of this fact, as the melting point of β-carbolines and their bromoderivatives are high (> 200°; see Table II and Experimental), experiments were performed at room temperature, without external control of the reaction temperature.

Table III
Static Charge Distribution for β-Carbolines and Bromo-β-carbolines and the Energy values of HOMO, LUMO and of LUMO relative to HOMO [a]

Compound	**1-C**	**3-C**	**4-C**	**4a-C**	**4b-C**	**5-C**	**6-C**	**7-C**	**8-C**	**8a-C**	**9a-C**	**HOMO/eV**	**LUMO/eV**	**Δ(LUMO-HOMO /eV)**
1	-0.087	-0.103	-0.127	-0.043	-0.087	-0.068	-0.162	-0.095	-0.157	0.036	-0.028	-8.645987	-0.403689	8.2423
	(-0.061)	(-0.089)	(-0.096)	(-0.036)	(-0.078)	(-0.041)	(-0.127)	(-0.074)	(-0.108)	(-0.115)	(-0.176)			
1a	-0.086	-0.102	-0.125	-0.043	-0.091	-0.039	-0.203	-0.068	-0.161	0.054	-0.024	-8.749132	-0.590462	8.1587
	(-0.059)	(-0.087)	(-0.093)	(-0.038)	(-0.073)	(-0.020)	(-0.136)	(-0.056)	(-0.103)	(-0.112)	(-0.177)			
1b	-0.088	-0.106	-0.123	-0.049	-0.090	-0.051	-0.170	-0.062	-0.209	0.077	-0.013	-8.685428	-0.599007	8.0864
1c	-0.084	-0.102	-0.122	-0.046	-0.093	-0.024	-0.211	-0.037	-0.212	0.087	-0.016	-8.823422	-0.793700	8.0297
1d	-0.084	-0.139	-0.091	-0.049	-0.091	-0.037	-0.203	-0.066	-0.161	0.060	-0.006	-8.827758	-0.749236	8.0785
1e	-0.079	-0.137	-0.091	-0.050	-0.090	-0.024	-0.208	-0.037	-0.209	0.0845	-0.006	-8.941401	-0.965648	7.9758
2	-0.025	-0.096	-0.133	-0.039	-0.087	-0.069	-0.162	-0.095	-0.157	0.035	-0.033	-8.549819	-0.377616	8.1722
	(-0.034)	(-0.083)	(-0.105)	(-0.030)	(-0.079)	(-0.041)	(-0.128)	(-0.074)	(-0.109)	(0.114)	(-0.174)			
2a	-0.023	-0.094	-0.130	-0.039	-0.091	-0.039	-0.203	-0.068	-0.161	0.053	-0.029	-8.658826	-0.564470	8.0944
2b	-0.025	-0.098	-0.129	-0.045	-0.098	-0.051	-0.170	-0.063	-0.209	0.076	-0.017	-8.588989	-0.566695	8.0223
2c	-0.021	-0.094	-0.128	-0.043	-0.093	-0.024	-0.212	-0.037	-0.213	0.088	-0.019	-8.723372	-0.756273	7.9671
2d	-0.021	-0.131	-0.096	-0.047	-0.092	-0.036	-0.204	-0.066	-0.163	0.062	-0.007	-8.721927	-0.713852	8.0081
2e	-0.014	-0.128	-0.097	-0.046	-0.091	-0.024	-0.209	-0.037	-0.210	0.085	-0.009	-8.845429	-0.924249	7.9212
3	-0.023	-0.093	-0.139	-0.028	-0.121	-0.034	-0.235	0.115	-0.192	0.068	-0.036	-8.569884	-0.329357	8.2405
	(-0.031)	(-0.080)	(-0.112)	(-0.018)	(-0.117)	(-0.001)	(-0.208)	(0.119)	(-0.156)	(0.079)	(-0.179)			
3a	-0.021	-0.090	-0.137	-0.026	-0.126	-0.012	-0.231	0.148	-0.246	0.088	-0.036	-8.658781	-0.491120	8.1677
3b	-0.023	-0.095	-0.135	-0.033	-0.127	-0.016	-0.246	-0.152	-0.245	0.106	-0.022	-8.576337	-0.477002	8.0993
3c	-0.019	-0.093	-0.129	-0.039	-0.100	-0.020	-0.223	0.143	-0.227	0.092	-0.022	-8.754094	-0.827326	7.9268
3d	-0.017	-0.099	-0.105	-0.031	-0.126	-0.010	-0.230	0.150	-0.248	0.093	-0.020	-8.755432	-0.651748	8.1037
3e	-0.014	-0.127	-0.098	-0.044	-0.098	-0.019	-0.221	0.144	-0.224	0.090	-0.011	-8.886707	-0.985159	7.9015
4	-0.028	-0.097	-0.134	-0.032	-0.127	-0.032	-0.193	0.121	-0.259	0.092	-0.022	-8.539757	-0.348652	8.1911
	(-0.030)	(-0.078)	(-0.112)	(-0.016)	(-0.120)	(-0.002)	(-0.169)	(0.131)	(-0.213)	(0.090)	(-0.020)			
4a	-0.025	-0.094	-0.134	-0.030	-0.129	-0.007	-0.236	0.151	-0.265	0.105	-0.023	-8.655602	-0.528344	8.1273
4b	-0.021	-0.094	-0.135	-0.031	-0.129	-0.016	-0.199	0.156	-0.306	0.113	-0.026	-8.674318	-0.556123	8.1182
5	-0.026	-0.097	-0.131	-0.035	-0.115	-0.037	-0.179	0.128	-0.239	0.080	-0.022	-8.692803	-0.596174	8.0966
	(-0.030)	(-0.079)	(-0.105)	(-0.027)	(-0.094)	(-0.017)	(-0.142)	(0.088)	(-0.171)	(0.090)	(-0.179)			
5a	-0.023	-0.093	-0.131	-0.033	-0.118	-0.014	-0.223	0.163	-0.247	0.093	-0.023	-8.771096	-0.742163	8.0289
5b	-0.023	-0.096	-0.130	-0.041	-0.097	-0.038	-0.174	0.131	-0.215	0.082	-0.021	-8.632413	-0.668747	7.9637
5d	-0.016	-0.127	-0.100	-0.041	-0.099	-0.031	-0.205	0.127	-0.168	0.069	-0.016	-8.779366	-0.805256	7.9741

[a] Calculations were performed using AM1 method and data in parenthesis by using PM3 method [20].

When very active substituents such as methoxy and methyl groups are present in the β-carboline moiety (harmine, **3**, Tables I and II) several bromo derivatives were obtained. Besides, the products obtained by bromination of harmine with NBS in 1:1 molar ratio, depend strongly on the reaction time. As it is shown in Table II, the formation of 6-bromo-harmine **3a** as only product was observed after 2 minutes while after 7 minutes almost all the harmine was converted to a mixture of the monobromo derivatives **3a** and **3b**. After 60 minutes the dibromo derivative **3c** was obtained together with **3a** and **3b** while after 80 minutes the dibromo derivative **3d** was also obtained together with **3a**, **3b** and **3c**.

Reducing the activity of the β-carboline moiety in the form of a milder hydrogen substitution, when the unsubstituted β-carboline species nor-harmane (**1**) was treated with NBS (1:1 molar ratio) and kept at room temperature in the dark, the regioselectivity of the reaction improved (Table II). Thus, the 6-bromo-nor-harmane **1a** was the bromo-β-carboline derivative obtained as the only product in high yield after 27 minutes of reaction. It was necessary to wait 95 minutes to observe the complete bromination of nor-harmane and to detect only traces of the 8-bromoderivative **1b** (Table II**).**

Electrostatic Charges.

The absence of bromomethyl derivatives as products formed by bromination of methyl-β-carbolines (harmane, harmine, harmol and 7-acetylharmol) and of oxidized products together with the observation of nuclear bromination in all cases and the dependence of the reactivity of the β-carbolines on the nature of their substituents, indicate that in both solution and in solid state an electrophilic substitution occurs as the most important process. If this is indeed the case, then the partial atomic charges on the ring C-atoms should correlate with the bromination selectivity. In all compounds, it is invariably observed that mono-bromination is effective on the most electron-rich ring C-atom. The charge of the ring C-atoms are given in Table III and in agreement with calculated values the negative charge is higher where mono-bromination is effective. Thus, the 6-bromo-β-carboline is the monoderivative obtained in higher yield from nor-harmane (**1**), harmane (**2**) and harmine (**3**) while the 8-bromo-β-carboline is preferentially formed from harmol (**4**) and 7-acetylharmol (**5**).

About di-brominated products, the formation of the 6,8-dibromo derivatives **1c**, **2c** and **3c** are also in agreement with the partial atomic charge calculated for the C-atoms of the corresponding mono-bromo precursors (Table III). On the contrary, the formation of di- and tri-bromo derivatives including Br as substituent at C-3 is not predicted by partial atomic charge values. As can be seen in Table I, the corresponding 3-bromo mono-derivatives of compounds **1**-**5** were not obtained in any experimental condition even when the β-carboline:NBS molar ratio was 1:2. For compounds **1**, **2**, and **3** polybromo derivatives including Br as substituent at C-3 were obtained as 3,6-dibromo derivatives (**1d**, **2d** and **3d**) and 3,6,8-tribromo derivatives (**1e**, **2e** and **3e**) when in solution the β-carboline:NBS molar ratio 1:2 was used. When NBS - silica gel was used as reagent (Table I, entries c, d, g, h, k and l) the reaction in general was not so regioselective as when NBS was the reagent (Table I, entries a, b, e, f, i and j). In the case of harmol (**4**) only mono-bromo derivatives were obtained (**4a** and **4b**) while 7-acetylharmol **5** yielded the 3,6-dibromo derivative **5d** (Table I, entries m, n, o and p).

Taking into account that the reactivity of the pyridine ring towards the electrofilic groups is minor than that of the benzene ring [15] and taking into account also its reactivity towards the nucleophilic groups [16] and the radicals [17] is necessary to postulate that the presence of Br as subtituent at C-6 and/or C-8 increase selectively the negative charge density at C-3, being as consequence this position preferentially substituted in the pyridine ring (Scheme 2). The increase of the charge density in the aromatic moiety owing to the presence of the Br substituents is clearly observed in the LUMO-HOMO energy values and also is reflected in the uv spectra. The LUMO-HOMO values diminish (Table III) and the λ_{max} shows a bathochromic shift [18]. As we stated before, the absence of derivatives that include Br as susbtituent in the methyl group of the 1-methyl-β-carbolines **2**-**5** and also in the C-1 of nor-harmane suggest that a radical mechanism would not be operating at least to explain the specific substitution at C-3 of monobromo and dibromo derivatives.

HOMO-LUMO Energies.

The molecular orbital energies have been computed in order to distinguish the relative reactivity of the β-carbolines studied. If the reaction follows a well-defined electrophilic subtitution pathway, the HOMO and LUMO levels should be able to give an insight into the reactivity and assist in predicting the feasibility of such reaction. As it is shown in Table III, the difference calculated between the HOMO and LUMO levels is in between 8.0966 and 8.2423 eV. Sarma and Nagaraju have recently suggested that when the substrate HOMO - LUMO energy difference is low (7.9 to 9.1 eV), the bromination of this substrate in solid state is feasible and when the LUMO - HOMO gap widens (9.1 to 9.8 eV), the reaction is more difficult [11,19]. In agreement with this suggestion, the HOM-LUMO differences calculated for β-carbolines match with the former group. Besides, it is interesting to note that among the many solid-solid and solid-gas reactions studied so far in the literature, bromination is one of the few reactions where a molecular property contributes significantly to the solid state reactivity [11,19].

Conclusions.

The comparison of the results obtained by bromination of β-carbolines in solution and in solid state showes that both NBS brominations are exclusively nuclear

brominating and that the latter, solid state NBS bromination reaction, is regioselective and can be used to get in high yield, monobrominated derivatives. Although the reactivity depends strongly upon the nature of the substituents, product selectivity depends on the β-carboline/NBS molar ratio and on the reaction time. The reaction proceeds preferentially by an electrophilic substitution pathway rather than by any free radical mediated mechanism, even when brominations are performed in solution. The solid state diffusion reaction presents an alternative to NBS solution chemistry in terms of product selectivity.

EXPERIMENTAL

Thin layer chromatography (tlc) analysis was performed with aluminium silica gel sheets (0.2 layer thickness, silica-gel 60 F254). Mass spectra (ms) were obtained under electron impact (70 eV). The ratios m/z and the relative intensities are reported. Products were isolated by preparative thick layer chromatography and flash - column chromatography which was carried out using silica gel 200-400 mesh 60Å and hexane, hexane-ethyl acetate and ethyl acetate-ethanol as eluents. Melting points are uncorrected. ^{1}H- and ^{13}C-nmr spectra were run in deuteriochloroform, deuteriochloroform/methanol-d_4 and dimethylsulfoxide-d_6 at 200 and 500 MHz. Chemical shifts are reported in ppm values, using tetramethylsilane as internal standard, and ^{13}C-nmr assignments were confirmed by using DEPT pulse sequence.

Dichloromethane, chloroform, ethanol, hexane, ethyl acetate and other reagents used were analytical grade. Solvents were freshly distilled and dried before using. nor-harmane, harmane, harmine, harmol and *N*-bromoccinimide were purchased from Aldrich. 7-Acetoxyharmol (**5**) was prepared according to the procedure described bellow.

7-Acetyloxy-1-methyl-9*H*-pyrido[3,4-*b*]indole (7-Acetylharmol) (**5**).

Compound **5** was obtained by acetylation of commercial 1-methyl-9*H*-pyrido[3,4-*b*]indol-7-ol (harmol, **4**). A mixture of harmol (204.7 mg, 1.03 mmol) and acetic anhydride (1.0 ml) in pyridine (0.5 ml) was stirred at room temperature during 20 hours. In order to prevent the hydrolysis of the acetyloxy group, addition of methanol and/or sodium bicarbonate aqueous solution was avoided. Instead of these chemicals, toluene was added in order to yield the pyridine - toluene azeotrope and then the system was evaporated *in vacuo*. The solid residue obtained was purified by silica-gel column chromatography eluted with ethyl acetate and ethyl acetate - ethanol mixtures. Compound **4** (205 mg, 83% yield) was obtained as white needles (ethanol), mp 155°; ^{1}H-nmr (deuteriochloroform/methanol-d_4): δ 8.46 (broad singlet (bs), 1H, NH), 8.32 (d, 1 H, 3-H, J = 5.4 Hz), 7.91 (d, 1H, 5-H, J = 8.7 Hz), 7.63 (d, 1 H, 4-H, J = 5.4 Hz), 7.20 (d, 1 H, 8-H, J = 2.0 Hz), 6.96 (dd, 1 H, 6-H, J = 8.7, 2.0 Hz), 2.77 (s, 3 H, CH_3), 2.39 ppm (s, 3 H, CH_3CO); ^{13}C-nmr (deuteriochloroform/methanol-d_4): δ 170.3 (CO), 150.8 (7-C), 141.4 (1-C), 140.2 (9a-C), 136.6 (3-C), 135.2 (8a-C), 127.9 (4b-C), 122.1 (5-C), 119.1 (4a-C), 113.8 (6-C), 112.6 (4-C), 104.7 (8-C), 20.9 (CH_3), 18.9 ppm (CH_3CO); hrms: Calc. for $C_{14}H_{12}N_2O_2$ 240.089878, found: 240.089947.

Anal. Calc. for $C_{14}H_{12}N_2O_2$: C, 69.98; H, 5.03; N, 11.66. Found: C, 69.96; H, 5.04; N, 11.65.

Bromination Reaction of β-Carbolines (**1-5**) with *N*-Bromosuccinimide.

To a stirred solution of β-carboline (100 mg, 0.50 mmoles) in dichloromethane (or ethyl acetate - ethanol) (50 ml) whether containing silica gel (1 g) or not depending on the bromination method used, a solution of *N*-bromosuccinimide (100 mg, 0.15 to 0.60 mmole , depending on the stoichiometry used) in dichloromethane (50 ml) was added dropwise. The reaction was stirred for an appropriate time in the absence of light at room temperature (or refluxed) until the tlc indicated that it was complete. All of these reactions were carried out under normal (air) atmosphere. The reaction mixture was then filtered and the silica-gel washed with dichloromethane (3 x 15 ml) and ethyl acetate - ethanol 1/1 (3 x 15 ml). The combined extracts were washed with sodium hydroxide 0.1 *N* (3 x 15 ml) and then with water (3 x 15 ml). The organic layer was dried over sodium sulfate, filtered and evaporated *in vacuo* to give a pale yellow solid residue. The residue was separated by flash column chromatography (silica gel-hexane-ethyl acetate-ethanol mixtures as eluent) to give as white solids (**1a**), (**1b**), (**1c**), (**1d**), (**1e**), (**2a**), (**2b**), (**2c**), (**2d**), (**2e**), (**3a**), (**3b**), (**3c**), (**3d**), (**3e**), (**4a**), (**4b**), (**5a**), (**5b**) and (**5d**) respectively. According to the experimental conditions used the percentage yield of the products obtained are different as it is described in Results and Discussion.

6-Bromonor-harmane (**1a**)

Compound **1a** has mp 263-265° (d) (lit 265-268° [7]); ^{1}H-nmr (dimethylsulfoxide-d_6): δ 11.76 (s, 1 H, NH), 8.92 (broad s (bs), 1H, 1-H), 8.50 (d, 1H, 5-H, J = 1.1 Hz), 8.35 (bs, 1H, 3-H), 8.15 (d, 1H, 4-H, J = 3.7 Hz), 7.66 (dd, 1H, 7-H, J = 8.8, 1.1 Hz), 7.56 ppm (d, 1H, 8-H, J = 8.8 Hz); ^{13}C-nmr (dimethylsulfoxide-d_6): δ 139.1 (9a-C), 138.3 (3-C), 134.7 (8a-C), 134.3 (1-C), 130.5 (7-C), 126.5 (4b-C), 124.3 (5-C), 122.4 (4a-C), 114.5 (6-C), 113.9 (4-C), 111.2 ppm (8-C); ms [1]: m/z 248 (^{81}Br, M^+, 43), 246 (^{79}Br, M^+, 43), 167 (32), 140 (36), 124 (10), 113 (20).

8-Bromonor-harmane (**1b**).

Compound **1b** has mp 248-250°; ^{1}H-nmr (deuteriochloroform/methanol-d_4): δ 11.90 (s, 1H, NH), 8.81 (bs, 1H, 1-H), 8.32 (bs, 1H, 3-H), 8.07 (d, 1H, 5-H, J = 8.0 Hz), 7.97 (d, 1H, 4-H, J = 5.1 Hz), 7.69 (d, 1H, 7-H, J = 7.7), 7.14 ppm (t, 1H, 6-H, J = 8.0, 7.7 Hz); ^{13}C-nmr (deuteriochloroform / methanol-d_4): δ 139.5 (9a-C), 137.4 (3-C), 133.7 (8a-C), 133.3 (1-C), 130.4 (7-C), 128.9 (4b-C), 123.0 (4a-C), 122.0 (6-C), 120.2 (5-C), 114.9 (4-C), 104.4 ppm (8-C); ms [1]: m/z 248 (^{81}Br, M^+, 90), 246 (^{79}Br, M^+, 100), 167 (56), 166 (23), 140 (54), 139 (34), 124 (12), 123 (13), 113 (27).

Anal. Calcd. For $C_{11}H_7N_2Br$: C, 53.47; H, 2.86; N, 11.34; Br, 32.33. Founds: C, 53.49; H, 2.85; N, 11.32; Br, 32.34.

6,8-Dibromonor-harmane (**1c**).

Compound **1c** has mp > 300° (d); ^{1}H-nmr (deuteriochloroform/methanol-d_4): δ 11.95 (bs, 1H, NH), 8.96 (bs, 1H, 1-H), 8.54 (d, 1H, 5-H, J = 1.5 Hz), 8.39 (bs, 1H, 3-H), 8.16 (d, 1H, 4-H, J = 4.7 Hz), 7.94 ppm (d, 1H, 7-H, J = 1.5 Hz); ^{13}C-nmr (dimethylsulfoxide-d_6/methanol-d_4): δ 138.9 (9a-C), 138.8 (3-C), 136.4 (8a-C), 134.9 (1-C), 131.9 (7-C), 126.2 (4b-C), 123.8 (5-C), 121.1 (4a-C), 115.4 (4-C), 111.1 (6-C), 106.5 ppm

(8-C); ms: m/z 328 ($^{81}Br/^{81}Br$, M^+, 11), 326 ($^{81}Br/^{79}Br$, M^+, 23), 324 ($^{79}Br/^{79}Br$, M^+, 15), 247 (6), 245 (6), 218 (2), 166 (28), 138 (13).

Anal. Calcd. For $C_{11}H_6N_2Br_2$: C, 40.52; H, 1.85; N, 8.59; Br, 49.02. Founds: C, 40.54; H, 1.84; N, 8.60; Br, 49.02.

3,6-Dibromonor-harmane (**1d**).

Compound **1d** has mp 273-275° (d); ^{1}H-nmr (dimethylsulfoxide-d_6): δ 11.90 (s, 1H, NH), 8.72 (bs, 1H, 1-H), 8.55 (bs, 1H, 5-H, J = 1.5), 8.46 (bs, 1H, 4-H), 7.70 (dd, 1H, 7-H, J = 8.0, 1.5 Hz), 7.58 ppm (d, 1H, 8-H, J = 8.0 Hz); ^{13}C-nmr (dimethylsulfoxide-d_6): δ 140.0 (9a-C), 135.9 (8a-C), 134.1 (1-C), 131.4 (7-C), 130.2 (3-C), 128.4 (4b-C), 124.8 (5-C), 121.4 (4a-C), 118.6 (4-C), 114.1 (8-C), 111.5 ppm (6-C); ms [1]: m/z 328 ($^{81}Br/^{81}Br$, M^+, 12), 326 ($^{81}Br/^{79}Br$, M^+, 26), 324 ($^{79}Br/^{79}Br$, M^+, 15), 247 (16), 245 (17), 218 (4), 166 (36), 165 (14), 139 (27), 138 (20).

Anal. Calcd. For $C_{11}H_6N_2Br_2$: C, 40.52; H, 1.85; N, 8.59; Br, 49.02. Founds: C, 40.55; H, 1.84; N, 8.57; Br, 49.04.

3,6,8-Tribromonor-harmane (**1e**).

Compound **1e** has mp 280-282° (d); ^{1}H-nmr (dimethylsulfoxide-d_6): δ 12.14 (s, 1H, NH), 8.73 (s, 1H, 1-H), 8.58 (s, 1H, 5-H), 8.47 (s, 1H, 4-H), 7.98 ppm (s, 1H, 7-H); ^{13}C-nmr (dimethylsulfoxide-d_6/methanol-d_4): δ 138.2 (9a-C), 135.9 (8a-C), 134.6 (1-C), 132.7 (7-C), 130.3 (3-C), 128.9 (4b-C), 124.5 (5-C), 122.4 (4a-C), 118.9 (4-C), 111.3 (6-C), 105.2 ppm (8-C); ms [1]: m/z 408 ($^{81}Br/^{81}Br/^{81}Br$, M^+, 13), 406 ($^{81}Br/^{81}Br/^{79}Br$, M^+, 39), 404 ($^{81}Br/^{79}Br/^{79}Br$, M^+, 37), 402 ($^{79}Br/^{79}Br/^{79}Br$, M^+, 15), 327 (16), 325 (24), 323 (17), 298 (4), 246 (28), 244 (30), 218 (4), 203 (4), 160 (3), 166 (13), 165 (52), 139 (12), 138 (43).

Anal. Calcd. For $C_{11}H_5N_2Br_3$: C, 32.63; H, 1.24; N, 6.92; Br, 59.20. Founds: C, 32.66; H, 1.23; N, 6.94; Br, 59.17.

6-Bromoharmane (**2a**).

Compound **2a** has mp 248-250° (d); ^{1}H-nmr (deuteriochloroform-methanol-d_4): δ 10.57 (s, 1H, NH), 8.14 (d, 1H, 3-H, J = 5.1 Hz), 8.13 (d, 1H, 5-H, J = 1.8 Hz), 7.68 (d, 1H, 4-H, J = 5.1 Hz), 7.53 (dd, 1H, 7-H, J = 8.6, 1.8 Hz), 7.36 (d, 1H, 8-H, J = 8.6 Hz), 2.72 ppm (s, 3H, CH_3); ^{13}C-nmr (deuteriochloroform/methanol-d_4): δ 142.2 (1-C), 139.4 (4a-C), 137.1 (3-C), 135.2 (8a-C), 130.9 (7-C), 127.3 (4b-C), 124.2 (5-C), 123.1 (4a-C), 113.9 (8-C), 112.9 (4-C), 112.3 (6-C), 19.3 ppm (CH_3); ms [1]: m/z 262 (^{81}Br, M^+, 17), 260 (^{79}Br, M^+, 18), 181 (11), 179 (6), 154 (8).

Anal. Calcd. For $C_{12}H_9N_2Br$: C, 55.20; H, 3.47; N, 10.73; Br, 30.60. Founds: C, 55.23; H, 3.46; N, 10.75; Br, 30.56.

8-Bromoharmane (**2b**).

Compound **2b** has mp 201-204° (d); ^{1}H-nmr (deuteriochloroform-methanol-d_4): δ 10.59 (s, 1H, NH), 8.26 (d, 1H, 3-H, J = 5.1 Hz), 8.02 (d, 1H, 5-H, J = 8.0 Hz), 7.70 (d, 1H, 4-H, J = 5.1 Hz), 7.67 (d, 1H, 7-H, J = 7.7 Hz), 7.13 (t, 1H, 6-H, J = 8.0, 7.7 Hz), 2.83 ppm (s, 3H, CH_3); ^{13}C-nmr (deuteriochloroform/-methanol-d_4): δ 142.3 (1-C), 139.0 (9a-C), 137.2 (3-C), 134.3 (8a-C), 130.4 (7-C), 127.4 (4b-C), 122.9 (4a-C), 122.7 (6-C), 120.5 (5-C), 112.8 (4-C), 104.5 (8-C), 18.9 ppm (CH_3); ms [1]: m/z 262 (^{81}Br, M^+, 84), 260 (^{79}Br, M^+, 100), 181 (32), 179 (22), 154 (30), 127 (12).

Anal. Calcd. For $C_{12}H_9N_2Br$: C, 55.20; H, 3.47; N, 10.73; Br, 30.60. Founds: C, 55.22; H, 3.46; N, 10.75; Br, 30.57.

6,8-Dibromoharmane (**2c**).

Compound **2c** has mp 248-250°; ^{1}H-nmr (deuteriochloroform/methanol-d_4): δ 10.70 (s, 1H, NH), 8.74 (d, 1H, 3-H, J = 5.5 Hz), 8.17 (d, 1H, 5-H, J = 1.1 Hz), 7.72 (d, 1H, 7-H, J = 1.1 Hz), 7.66 (d, 1H, 4-H, J = 5.5 Hz), 2.76 ppm (s, 3H, CH_3); ^{13}C-nmr (deuteriochloroform/methanol-d_4): δ 144.3 (1-C), 138.6 (2-C), 136.2 (9a-C), 133.7 (7-C), 132.0 (8a-C), 128.8 (4b-C), 125.1 (4a-C), 124.1 (5-C), 114.1 (4-C), 112.9 (6-C), 106.4 (8-C), 20.2 ppm (CH_3); ms [1]: m/z 343 ($^{81}Br/^{81}Br$, M^+, 17), 341 ($^{81}Br/^{79}Br$, M^+, 45), 339 ($^{79}Br/^{79}Br$, M^+, 100), 312 (4), 262 (9), 261 (14), 260 (11), 259 (14), 234 (6), 232 (7), 180 (34), 179 (26), 170 (9), 168 (6), 153 (13), 152 (17).

Anal. Calcd. For $C_{12}H_8N_2Br_2$: C, 42.39; H, 2.37; N, 8.24; Br, 47.00. Founds: C, 42.42; H, 2.39; N, 8.26; Br, 46.93.

3,6-Dibromoharmane (**2d**).

Compound **2d** has mp 255-257° (d); ^{1}H-nmr (deuteriochloroform/methanol-d_4): δ 10.65 (s, 1H, NH), 8.04 (d, 1H, 5-H, J = 1.8 Hz), 7.78 (s, 1H, 4-H), 7.54 (dd, 1H, 7-H, J = 8.8, 1.8 Hz), 7.33 (d, 1H, 8-H, J = 8.8 Hz), 2.68 ppm (s, 3H, CH_3); ^{13}C-nmr (deuteriochloroform/methanol-d_4): δ 143.6 (1-C), 140.6 (9a-C), 135.1 (8a-C), 131.9 (7-C), 130.5 (3-C), 127.9 (4b-C), 124.6 (5-C), 122.4 (4a-C), 116.6 (4-C), 113.9 (8-C), 112.8 (6-C), 19.5 ppm (CH_3); ms [1]: m/z 343 ($^{81}Br/^{81}Br$, M^+, 17), 341 ($^{81}Br/^{79}Br$, M^+, 45), 339 ($^{79}Br/^{79}Br$, M^+, 100), 262 (12), 260 (37), 259 (36), 234 (6), 323 (7), 180 (50), 179 (53), 170 (10), 153 (22), 152 (20).

Anal. Calcd. For $C_{12}H_8N_2Br_2$: C, 42.60; H, 2.37; N, 8.28; Br, 46.75. Founds: C, 42.62; H, 2.35; N, 8.29.

3,6,8-Tribromoharmane (**2e**).

Compound **2e** has mp 233-235° (d); ^{1}H-nmr (deuteriochloroform-methanol-d_4): δ 8.31 (bs, 1H, NH), 8.09 (d, 1H, 5-H, J = 1.8 Hz), 7.88 (s, 1H, 4-H), 7.83 (d, 1H, 7-H, J = 1.8 Hz), 2.83 ppm (s, 3H, CH_3); ^{13}C-nmr (deuteriochloroform/methanol-d_4): δ 144.1 (1-C), 138.0 (9a-C), 133.4 (7-C), 131.3 (8a-C), 130.5 (3-C), 128.6 (4b-C), 123.3 (5-C), 121.1 (4a-C), 116.4 (4-C), 112.3 (6-C), 105.5 (8-C), 19.5 ppm (CH_3); ms [1]: m/z 422 ($^{81}Br/^{81}Br/^{81}Br$, M^+, 31), 420 ($^{81}Br/^{81}Br/^{79}Br$, M^+, 87), 418 ($^{81}Br/^{79}Br/^{79}Br$, M^+, 88), 416 ($^{79}Br/^{79}Br/^{79}Br$, M^+, 33), 343 (7), 341(29), 339 (63), 312 (6), 262 (6), 261 (24), 260 (19), 259 (33), 234 (5), 232 (5), 210 (9),180 (37), 179 (73), 170 (45), 168 (8), 153 (18), 152 (33), 151 (30).

Anal. Calcd. For $C_{12}H_7N_2Br_3$: C, 34.40; H, 1.68; N, 6.68; Br, 57.22. Founds: C, 34.42; H, 1.69; N, 6.70; Br, 57.19.

6-Bromoharmine (**3a**).

Compound **3a** has mp 288-290° (d); ^{1}H-nmr (dimethylsulfoxide-d_6): δ 11.60 (s, 1H, NH), 8.44 (s, 1H, 5-H), 8.17 (d, 1H, 3-H, J = 5.5 Hz), 7.87 (d, 1H, 4-H, J = 5.5 Hz), 7.15 (s, 1H, 8-H), 3.97 (s, 3H, CH_3O); 2.73 ppm (s, 3H, CH_3); ^{13}C-nmr (dimethylsulfoxide-d_6): δ 155.4 (7-C), 141.6 (1-C), 140.9 (9a-C), 138.0 (3-C), 134.6 (8a-C), 126.4 (5-C), 125.7 (4b-C), 115.7 (4-C), 112.3 (4a-C), 103.1 (6-C), 94.9 (8-C), 56.3 (CH_3O), 20.3 ppm (CH_3); ms: m/z 292 (^{81}Br, M^+, 33), 290 (^{79}Br, M^+, 32), 277 (7), 275 (7), 249 (19), 247 (23), 211 (1), 210 (1), 196 (19), 181 (11), 168 (16), 152 (5), 140 (15).

Anal. Calcd. For $C_{13}H_{11}N_2OBr$: C, 53.63; H, 3.81; N, 9.62; Br, 27.44. Founds: C, 53.60; H, 3.80; N, 9.61; Br, 27.46.

8-Bromoharmine (**3b**).

Compound **3b** has mp 206-208°; ^{1}H-nmr (deuteriochloroform): δ 11.70 (s, 1H, NH), 8.37 (d, 1H, 3-H, J = 5.5 Hz), 7.99 (d, 1H, 5-H, J = 8.4 Hz), 7.73 (d, 1H, 4-H, J = 5.5 Hz), 6.96 (d, 1H, 6-H, J = 8.4), 4.04 (s, 3H, CH_3O), 2.85 ppm (s, 3H, CH_3); ^{13}C-nmr (deuteriochloroform/methanol-d_4): δ 156.3 (7-C), 141.7 (1-C), 138.4 (3-C), 130.9 (9a-C), 129.3 (8a-C), 128.7 (4b-C), 121.3 (5-C), 117.0 (4a-C), 112.6 (4-C), 105.8 (6-C), 93.0 (8-C), 56.9 (CH_3O), 19.5 ppm (CH_3); ms: m/z 292 (^{81}Br, M^+, 85), 290 (^{79}Br, M^+, 100), 277 (32), 275 (35), 249 (44), 247 (51), 211 (1), 210 (2), 196 (6), 181 (13), 168 (20), 152 (6), 140 (17).

Anal. Calcd. For $C_{13}H_{11}N_2OBr$: C, 53.63; H, 3.81; N, 9.62; Br, 27.44. Founds: C, 53.64; H, 3.80; N, 9.63; Br, 27.47.

6,8-Dibromoharmine (**3c**).

Compound **3c** has mp 208-210° (d); ^{1}H-nmr (deuteriochloroform): δ 11.90 (s, 1H, NH), 8.20 (d, 1H, 3-H, J = 5.5 Hz), 8.16 (s, 1H, 5-H), 7.65 (d, 1H, 4-H, J = 5.5 Hz), 3.93 (s, 3H, CH_3O), 2.78 ppm (s, 3H, CH_3); ^{13}C-nmr (dimethylsulfoxide): δ 152.6 (7-C), 143.2 (9a-C), 139.6 (1-C), 138.6 (3-C), 135.1 (8a-C), 126.7 (4b-C), 124.8 (5-C), 119.9 (4a-C), 112.8 (4-C), 107.8 (6-C), 100.1 (8-C), 60.8 (CH_3O), 20.8 ppm (CH_3); ms: m/z 372 (^{81}Br/^{81}Br, M^+, 12), 370 (^{81}Br/^{79}Br, M^+, 25), 368 (^{79}Br/^{79}Br, M^+, 13), 357 (6), 355 (11), 353 (5), 326 (17), 324 (7), 292 (1), 290 (1), 276 (11), 275 (5), 261 (4), 260 (4), 248 (7), 246 (8), 210 (5), 180 (33), 167 (19), 166 (18), 152 (5), 140 (26).

Anal. Calcd. For $C_{13}H_{10}N_2OBr_2$: C, 42.20; H, 2.72; N, 7.57; Br, 43.19. Founds: C, 42.21; H, 2.71; N, 7.58; Br, 43.22.

3,6-Dibromoharmine (**3d**).

Compound **3d** has mp 278-280° (d); ^{1}H-nmr (deuteriochloroform): δ 11.40 (s, 1H, NH), 8.08 (s, 1H, 5-H), 7.72 (s, 1H, 4-H), 6.94 (s, 1H, 8-H), 3.92 (s, 3H, CH_3O), 2.64 ppm (s, 3H, CH_3); ^{13}C-nmr (dimethylsulfoxide): δ 155.9 (7-C), 142.1 (9a-C), 141.7 (1-C), 134.3 (8a-C), 129.9 (3-C), 127.9 (4b-C), 126.2 (5-C), 115.4 (4-C), 114.7 (4a-C), 103.6 (6-C), 94.7 (8-C), 56.3 (CH_3O), 19.8 ppm (CH_3); ms: m/z 372 (^{81}Br/^{81}Br, M^+, 12), 370 (^{81}Br/^{79}Br, M^+, 24), 368 (^{79}Br/^{79}Br, M^+, 13), 357 (1), 355 (2), 353 (1), 326 (9), 324 (4), 292 (2), 291 (6), 276 (1), 275 (5), 261 (4), 260 (4), 248 (5), 246 (5), 210 (2), 195 (10), 194 (3), 180 (9), 167 (14), 166 (12), 152 (8), 140 (17).

Anal. Calcd. For $C_{13}H_{10}N_2OBr_2$: C, 42.20; H, 2.72; N, 7.57; Br, 43.19. Founds: C, 42.19; H, 2.71; N, 7.58; Br, 43.21.

3,6,8-Tribromoharmine (**3e**).

Compound **3e** has mp 248-250° (d); ^{1}H-nmr (deuteriochloroform): δ 9.48 (bs, 1H, NH), 8.15 (s, 1H, 5-H), 7.48 (s, 1H, 4-H), 3.96 (s, 3H, CH_3O), 2.79 ppm (s, 3H, CH_3); ^{13}C-nmr (deuteriochloroform): δ 154.2 (7-C), 143.4 (1-C), 140.0 (9a-C), 136.5 (8a-C), 130.1 (4b-C), 129.4 (3-C), 124.9 (5-C), 119.1 (4a-C), 116.3 (4-C), 109.7 (6-C), 100.5 (8-C), 61.2 (CH_3O); 19.9 ppm (CH_3); ms: m/z 452 (^{81}Br/^{81}Br/^{81}Br, M^+, 23), 450 (^{81}Br/^{81}Br/^{79}Br, M^+, 15), 448 (^{81}Br/^{79}Br/^{79} Br, M^+, 53), 446 (^{79}Br/^{79}Br/^{79}Br, M^+, 100), 437 (29), 406 (54), 371 (75).

Anal. Calcd. For $C_{13}H_9N_2OBr_3$: C, 34.78; H, 2.02; N, 6.24; Br, 53.40. Founds: C, 34.76; H, 2.01; N, 6.25; Br, 53.43.

6-Bromoharmol (**4a**).

Compound **4a** has mp 236-238°; ^{1}H-nmr (deuteriochloroform/methanol-d_4): δ 11.60 (s, 1H, NH), 8.08 (s, 1H, 5-H), 8.06 (d, 1H, 3-H, J = 5.5 Hz), 7.58 (d, 1H, 4-H, J = 5.5 Hz), 6.97 (s, 1H, 8-H), 2.67 ppm (s, 3H, CH_3); ^{13}C-nmr (deuteriochloroform/methanol-d_4): δ 154.2 (7-C), 141.7 (1-C), 140.7 (9a-C), 136.5 (3-C), 130.8 (8a-C), 128.0 (4b-C), 125.2 (5-C), 115.7 (4a-C), 111.9 (4-C), 103.4 (6-C), 97.4 (8-C), 18.5 ppm (CH_3); ms: m/z 278 (^{81}Br, M^+, 85), 276 (^{79}Br, M^+, 100), 249 (4), 198 (40), 196 (33), 170 (23), 169 (25), 152 (4), 140 (16), 127 (7), 115 (12), 99 (29), 84 (41), 77 (13).

Anal. Calcd. For $C_{12}H_{10}N_2OBr$: C, 51.82; H, 3.62; N, 10.07; Br, 28.73. Founds: C, 51.85; H, 3.61; N, 10.06; Br, 28.76.

8-Bromoharmol (**4b**).

Compound **4b** has mp 193-195° (d); ^{1}H-nmr (deuteriochloroform/methanol-d_4): δ 11.60 (s, 1H, NH), 8.18 (d, 1H, 4-H, J = 5.5 Hz), 7.84 (d, 1H, 5-H, J = 8.4 Hz), 7.70 (d, 1H, 3-H, J = 5.5 Hz), 7.21 (sa, 1H, OH), 6.91 (d, 1H, 6-H, J = 8.4 Hz), 2.83 ppm (s, 3H, CH_3); ^{13}C-nmr (dimethylsulfoxide-d_6): δ 154.6 (7-C), 142.1 (1-C), 141.0 (9a-C), 138.2 (3-C), 134.4 (8a-C), 128.5 (4b-C), 121.1 (5-C), 115.1 (4a-C), 111.8 (4-C), 109.7 (6-C), 90.8 (8-C), 20.6 ppm (CH_3); ms: m/z 278 (^{81}Br, M^+, 75), 276 (^{79}Br, M^+, 100), 249 (5), 198 (46), 196 (53), 170 (23), 169 (18), 152 (5), 140 (17).

Anal. Calcd. For $C_{12}H_{10}N_2OBr$: C, 51.82; H, 3.62; N, 10.07; Br, 28.73. Founds: C, 51.80; H, 3.61; N, 10.05; Br, 28.76.

6-Bromo-7-acetylharmol (**5a**).

Compound **5a** has mp 276-278°; ^{1}H-nmr (deuteriochloroform/methanol-d_4): δ 11.60 (s, 1H, NH), 8.19 (d, 1H, 3-H, J = 5.4), 8.15 (s, 1H, 5-H), 7.58 (d, 1H, 4-H, J = 5.4 Hz), 7.24 (s, 1H, 8-H), 2.72 (s, 3H, CH_3), 2.59 ppm (s, 3H, CH_3CO); ^{13}C-nmr (deuteriochloroform/methanol-d_4): δ 169.8 (CO), 147.4 (7-C), 142.1 (1-C), 139.8 (9a-C), 137.8 (3-C), 137.4 (8a-C), 126.7 (4b-C), 125.6 (5-C), 120.9 (4a-C), 112.6 (4-C), 106.8 (6-C), 106.6 (8-C), 20.9 (CH_3), 19.5 ppm (CH_3CO); ms: m/z 320 (^{81}Br, M^+, 85), 318 (^{79}Br, M^+, 100), 275 (45), 273 (23), 194 (35), 179 (15).

Anal. Calcd. For $C_{14}H_{11}N_2O_2Br$: C, 52.69; H, 3.47; N, 8.78; Br, 25.04. Founds: C, 52.66; H, 3.48; N, 8.80; Br, 25.08.

8-Bromo-7-acetylharmol (**5b**).

Compound **5b** has mp 220-222°; ^{1}H-nmr (deuteriochloroform/methanol-d_4): δ 8.42 (s, 1H, NH), 8.39 (d, 1H, 3-H, J = 5.5 Hz), 7.88 (d, 1H, 5-H, J = 8.4 Hz), 7.68 (d, 1H, 4-H, J = 5.5 Hz), 7.03 (d, 1H, 6-H, J = 8.4 Hz), 2.84 (s, 3H, CH_3), 2.45 ppm (s, 3H, CH_3CO); ^{13}C-nmr (deuteriochloroform/methanol-d_4): δ 168.9 (CO), 148.0 (7-C), 142.4 (1-C), 139.9 (9a-C), 139.6 (3-C), 134.7 (8a-C), 128.5 (4b-C), 120.8 (4a-C), 121.1 (5-C), 115.8 (6-C), 113.0 (4-C), 98.9 (8-C), 20.8 (CH_3), 20.3 ppm (CH_3CO); ms: m/z 320 (^{81}Br, M^+, 80), 318 (^{79}Br, M^+, 100), 275 (40), 273 (25), 194 (15), 179 (10).

Anal. Calcd. For $C_{14}H_{11}N_2O_2Br$: C, 52.69; H, 3.47; N, 8.78; Br, 25.04. Founds: C, 52.68; H, 3.46; N, 8.80; Br, 25.07.

3,6-Dibromo-7-acetylharmol (**5d**).

Compound **5d** was obtained as a syrup; ^{1}H-nmr (deuteriochloroform): δ 8.54 (s, 1H, NH), 7.83 (s, 1H, 5-H), 7.53 (s, 1H, 4-H), 7.06 (s, 1H, 8-H), 2.69 (s, 3H, CH_3), 2.51 ppm (s, 3H, CH_3CO); ms: m/z 400 (^{81}Br/^{81}Br, M^+, 12), 398 (^{81}Br/^{79}Br, M^+, 26), 396 (^{79}Br/^{79}Br, M^+, 18), 353 (15), 338 (22), 257 (18), 176 (10),

Anal. Calcd. For $C_{14}H_{10}N_2O_2Br_2$: C, 42.24; H, 2.53; N, 7.04; Br, 40.15. Founds: C, 42.26; H, 2.52; N, 7.06; Br, 40.19.

Solid State Reactions.

The substrate (~1.0 g) and freshly powdered NBS (1:1 molar equivalents) were mixed very gently for a few seconds. After the specific reaction time the mixture was dissolved in ethyl acetate and the reaction was monitored by tlc as usual. Then the reaction mixture was separated by flash column chromatography (silica gel - hexane - ethyl acetate and ethyl acetate - ethanol mixtures as eluent). All the products obtained were characterized by mp, ^{1}H-nmr, ^{13}C-nmr and ms.

According to the experimental conditions used the percentage conversion of β-carbolines are different as can be seen in Table II. Either grinding of the mixture or monitoring the reaction for a longer time did not result in a paste, because of the high melting point of reactants and products involved.

Calculations.

The ground-state geometry, heat of formation and static charge distribution for predicting chemical reactivity of β-carbolines **1**-**5**, bromo-β-carbolines and possible reaction intermediates were calculated by using the semiempirical parametrized AM1 and PM3 method as implemented in version of the HyperChem program [20]. The HOMO and LUMO calculations were performed by using the same semiempirical methods (Table III).

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